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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/206,132	12/07/98	FREEMAN G	RPI-008CPDV

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EXAMINER	
NGUYEN,Q	

ART UNIT	PAPER NUMBER
1632	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/206,132	FREEMAN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen	1632	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42,43 and 46-87* is/are pending in the application.

4a) Of the above claim(s) *42,43,46-60,64-70 and 75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-63,71-74 and 76-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Applicants' election of Group II (claims 61-63, 71-74 and 76-87) **without traverse**, in Paper No. 13 is acknowledged. The elected invention is drawn to a method for treating a subject with a tumor by modifying tumor cells *in vivo* using a nucleic acid molecule encoding B7-2, and a method of modifying tumor cells *in vivo* using a nucleic acid molecule encoding for B7-2 molecule alone or in combinations with nucleic acid molecules encoding for B7 protein, MHC class II alpha and beta chain proteins, MHC class I alpha chain protein, beta-2 microglobulin protein, or an anti-agonist of MHC class II associated protein, classified in class 514, subclass 44.

Claims 42, 43, 46-60, 64-70 and 75 are withdrawn from further consideration in the present application because they are drawn to non-elected inventions.

Claims 61-63, 71-74 and 76-87 are examined on the merits herein.

Claim Objections

Claim 78 is objected to because of the following informalities: a space should be inserted between α and chain for the term "αchain" recited in the claim. Appropriate correction is required.

Claim 87 is objected to because of the following informalities: "immunogenecity" is misspelled and it should be replaced by - - immunogenicity - -. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 61-62, 71-74 and 76-87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a mammalian subject having **a solid tumor**, comprising **direct administering** into said tumor a nucleic acid encoding a mammalian B7-2 molecule in a form suitable for expression of the B7.2 molecule in tumor cells of said tumor and wherein **said B7.2 molecule has the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4 ligand** such that the growth of said tumor is inhibited; the same method for modifying a tumor cell *in vivo* or for increasing the immunogenecity of a tumor cell *in vivo*, does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 61-62 and 71-72 are drawn to a method for treating a subject with a tumor comprising modifying tumor cells *in vivo* to express a T cell costimulatory molecule, B7-2, by delivering to the subject a nucleic acid molecule encoding for B7-2.

Claims 71-74 and 76-86 are drawn to a method of modifying a tumor cell to express a B7-2 molecule comprising transfecting a tumor cell with a nucleic acid molecule encoding a B7-2 molecule such that B7-2 is expressed by the tumor cell; the same method wherein the tumor cells are further transfected with at least one nucleic acid molecule encoding at least one MHC class II α chain protein and at least one MHC class II β chain protein, or wherein the tumor cells are further transfected with at least one nucleic acid molecule encoding at least one MHC class I α chain protein, or wherein the tumor cells are further transfected with a nucleic acid encoding a β-2 microglobulin protein, or wherein the tumor cells are further transfected with a nucleic acid molecule which is anti-sense to a regulatory or a coding region of the invariant chain gene and thereby inhibiting the expression the MHC class II associated protein.

Claim 87 is directed to a method of increasing the immunogenecity of a tumor cell comprising modifying the tumor cell to express a B7-2 T cell costimulatory molecule such that the immunogenicity of the tumor cell is increased.

With regard to the elected invention, the instant specification discloses that tumor cells could be modified *in vivo* by introducing a nucleic acid molecule encoding B7-2 into the tumor cells for expression of the co-stimulatory molecule on the surface of tumor cells. Similarly, nucleic acid molecules encoding MHC class I or class II molecule or an antisense sequence of a MHC class II associated protein or the invariant chain gene (Ii

gene) could also be introduced into tumor cells *in vivo* (See specification, pages 18-19). However, such disclosure is not deemed to be sufficient guidance for one skilled in the art at the effective filing date of the present application to make and use the instant broadly claimed invention for the reasons to be discussed below.

The nature of the elected invention for the instant claims falls within the realm of gene therapy, specifically *in vivo* gene therapy. At the effective filing date of the present application, the art of gene therapy was immature and highly unpredictable. In reviewing the state of the gene therapy art at about the time of the instant invention, Marshall (Science 269:1050-1055, 1995) stated that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (page 1050, column 1, lines 5-9 of the last paragraph) and that "with more than 100 clinical trials started and hundreds of millions of dollars at stake, the field is struggling to meet expectations" (page 1050, subtitle). In the same review article, NIH director Harold Varmus was quoted as saying "Despite the growing support for gene therapy, the field remains at a very early stage of development. While there are several reports of convincing gene transfer and expression, there is still little or no evidence of therapeutic benefit in patients – or even in animal models" (page 1050, column 2, first full paragraph). Even in a meeting review article on gene therapy and translational cancer research many years after the effective filing date of the present application, Dang et al. (Clin. Cancer Res. 5:471-474, 1999) stated that "This workshop reviewed some recent advances in gene delivery, gene expression, immune manipulation, and the development of molecular targets and stressed that all of these fields will need further advancement **to**

make gene therapy a reality" (page 471, column 1, last sentence of first paragraph). Thus, it is clear that the art of gene therapy at the effective filing date of the instant invention was still immature, unpredictable and that the obstacles associated with gene therapy for achieving therapeutic effects could not have been overcome with routine experimentation.

With respect to claims 73-74 and 76-87, although there is no recitation for therapeutic effects, when read in light of the specification the sole purpose for modifying a tumor cell *in vivo* comprising the transfection of a tumor cell with a nucleic acid encoding a B7-2 molecule and for increasing the immunogenicity of a tumor cell *in vivo* is for treating a patient with a tumor, encompassing the inhibition or eradication of tumor growth, preventing or inhibiting tumor metastasis or inhibiting the recurrence of a tumor. The instant specification is not enabled for the broadly claimed invention because it fails to provide sufficient guidance demonstrating that any therapeutic effects has been achieved for treating a patient having a tumor by delivering to the patient a nucleic acid molecule encoding B7-2 molecule or in combinations with other nucleic acid molecules as claimed. The mere exemplification (Example 5) showing that no tumor growth was observed upon intradermal or subdermal implantation of J558 plasmacytoma cells transfected *in vitro* with an expression vector containing cDNA encoding either mouse B7-2 or B7-1 molecule in syngeneic Balb/c mice is not deemed to have a reasonable correlation with the entire scope of the instant elected invention. The instant claims encompass any and all routes of delivering a nucleic acid molecule encoding a B7-2 molecule alone or in combinations with a nucleic acid molecule encoding a B7 protein, a

MHC class I or class II molecule, or an antisense sequence of the invariant chain gene into a subject having a tumor for treating or modifying or increasing the immunogenicity of tumor cells. However, at the effective filing date of the present application, *in vivo* vector targeting to desired cells, tissues or organs, for this instance tumor cells, continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art, including those published several years after the effective filing date of the present application. For examples, Miller & Vile (FASEB 9:190-199, 1995) reviewed the types of vectors available for *in vivo* gene therapy, and concluded that ""for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances .... Targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (Exp. Opin. Ther. Patents 8:53-69, 1998) indicated that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain also reviewed new techniques under experimentation in the art which show promise, but is currently even less efficient than viral gene delivery (see page 65, first pargraph under Conclusion section). Verma & Somia (Nature 389:239-242,1997) reviewed various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see the entire article). Verma & Somia discussed the role of the

immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239, and second and third columns of page 242). Verma & Somia also indicated that appropriate enhancer-promoter sequences can improve expression, but that the "search for such combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). The instant specification fails to teach a skilled artisan how to overcome the unpredictability for vector targeting *in vivo* known in the art such that efficient gene transfer and expression of encoded molecules such as B7-2 protein, B7 protein, MHC class I or class II molecule, or an antisense sequence of the invariant chain gene could be achieved in tumor cells of a subject by any and all modes of delivery. With respect to non-solid tumors, e.g. leukemia, the instant specification also fails to provide any guidance for overcoming the adverse host immune reactions against recombinant viral vectors, particularly recombinant adenovirus vectors, as noted by Verma & Somia above such that an effective transgene delivery and expression could be achieved in such tumor cells to attain the desired therapeutic effects. In the absence of such guidance provided by the instant specification, it would have required undue experimentation without a predictable expectation of success for one skilled in the art to make and use the broadly claimed invention.

There are several factors known to limit an effective gene therapy, among which include the lack of an optimal vector and the lack of a stable transgene expression *in vivo*. In a recent review many years after the effective filing date of the present application (Methods of gene delivery, Hematol. Oncol. Clin. North Am. 12:483-501,

1998), Wivel & Wilson stated that "One of the major challenges still confronting the field is the design of more efficient vectors. The gene delivery systems being used today will undoubtedly be seen as crude when compared with future developments. It is unlikely that there will ever be a universal vector, but rather there will be multiple vectors specifically designed for certain organ sites and certain diseases...It will be necessary to do much more fundamental research in cell biology, virology, immunology, and pathophysiology before vectors can be significantly improved." (pages 498-499 in Summary section). Additionally, factors such as the level of mRNA produced, the stability of the protein produced, the protein's proper compartmentalization within the cell or its secretory fate differ dramatically based on which protein being produced, and therefore the desirable therapeutic effects sought to achieve (Eck & Wilson, Gene-based therapy, 1996; page 82, col. 1, first paragraph). Thus, the level of gene expression *in vivo*, its duration, and its *in vivo* therapeutic effects can not be predictable, nor they can be overcome with routine experimentation. With respect to the breadth of the claims encompassing any and all genes encoding a MHC class I or class II protein, any and all antisense nucleic acid molecules inhibiting the expression of an MHC class II associated protein, in addition to a nucleic acid encoding a B7-2 protein or B7 protein, the instant specification fails to provide sufficient guidance for one skilled in the art how to overcome the obstacles and the unpredictability associated with gene therapy such that a stable and effective expression for the various aforementioned molecules in conjunction with the B7-2 expression in tumor cells could be achieved *in vivo* to attain the desired therapeutic effects (presumably **additional or synergistic effects)**

contemplated by the instant invention. Furthermore, with regarding to claims 81 and 82, the specification fails to provide any guidance showing that any effective antisense nucleic acid molecule could be obtained in inhibiting the expression of the invariant chain in tumor cells *in vivo* to achieve the desired therapeutic effects despite the many unwanted non-antisense effects known to be associated with the antisense strategy (Branch A.D., TIBS 23:45-50, 1998). Although Branch noted that certain non-antisense effects can yield therapeutic effects, however, these non-antisense effects are not predictable even in 1998 and rules for rational design can not be applied to the production of non-antisense drugs and therefore they must be explored on a case-by-case basis (column 1, page 50).

Accordingly, due to the lack of direction, guidance provided by the specification regarding to the issues raised above, the unpredictability of the gene therapy art, and the breadth of the claims, it would have required undue experimentation without a predictable degree of success for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 61-63 and 71-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

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